REMARKS

In response to the informalities in the claims, the terms "plasma discharge" have been removed from the claims. However, to observe the formalities, a comma has been left between the term "infection" and "and."

Concerning the Examiner's claim rejections under 35 U.S.C. § 112, Claim 1 has been changed to replace "the" with "a" in line 2.

In further response to the Examiner's rejections under 35 U.S.C. § 112, Claim 1 has been changed in an effort to (a) provide the antecedent basis of protein analyte, and (b) make clear the identities of the solutions referred to in the claim; these changes consequently result in a better description of the invention.

The claim describes a method that allows the identification of a protein that is contained inside a microbe (and thus not able to bind to tethered peptide ligands when the microbe is intact). The intent is to describe the identification of these intracellular proteins by (1) breaking open the microbe, thereby allowing the "microbial guts" (and protein analyte of interest) to spill into the solution in which the microbial cells are suspended; (2) exposing this solution (now containing these cytosolic proteins and any intact microbes) to a peptide ligand-tethered substrate surface resulting in the specific capture of the protein analyte by the ligands; (3) physically separating the substrate from the ruptured microbe/"microbe guts" solution and washing this surface to remove non-binding components; and (4) interrogating the surface for protein binding via intrinsic fluorescence. To describe this process, the claim has been amended.

In response to the Examiner's rejection as failing to comply with the written description requirement, the subject matter "plasma discharge" has been removed from the amended claim.

In response to the Examiner's rejection under 35 U.S.C. § 103 as being unpatentable over Powers, et al. and further in view of the teachings of Waskiewicz and Trudil, Applicants respectfully submit the following:

On pages 8-9, Powers et al. (WO 98/49557) teaches the "taxonomic identification of microorganisms in which microbes are captured through the binding of microbial receptors to specific ligands tethered to a surface" where the receptor examples include *"a protein residing in the outer membrane of the microbial cell,* pilus or flagellum which is exposed to the aqueous environment surrounding the cell" (not cytosolic proteins present in the interior of the cell). (However, Powers, et al. does teach a protein analyte sample [pg. 10, lines 1-2] when it states, "capture of microorganisms, peptides or proteins contained in the sample.") Powers, et al. does not teach (1) the steps of washing away non-bound portions of the sample (biological components of the matrix from which the analyte was captured), (2) the use of photostable linkers, (3) nor the indicated tether lengths that are to be used for each kind of biological analyte.

Fodor, et al. (U.S. Patent 6,124,102) teaches the use of their VLSIPS (very large scale immobilized polymer synthesis) methodology to determine binding between ligands (including peptide ligands) and various receptors (abstract). The essence of the invention disclosed by Fodor, et al. (when utilizing peptide ligands) is a way of synthesizing patches of surface-tethered peptide ligands, with each patch area containing ligands that have different sequences. Using the VLSIPS methodology, one is taught to utilize photo-activated cross-linker chemistry to synthesize peptides of various lengths and chemical composition; it will be appreciated by one skilled in the art that this is essentially another way of teaching the synthesis of peptides of

varying sequences. However, as cited by the examiner, Fodor, et al. does teach (col. 18, lines 19-27) that the length and chemical composition of the linker (between the surface and ligand) is varied to optimize the binding between the ligand and the receptor. In the case where the ligand is a drug, hapten, or other small molecule, VLSIPS-synthesized peptides are used as the linkers. In the method taught by Fodor, et al., linker length and chemical composition are optimized for the maximum binding interaction between ligand and dye-conjugated receptor. (It is important to note that Fodor teaches using dye-labeled receptors [col. 29, lines 52-55]; the use of dye-conjugated receptors is necessary to detect the presence and extent of binding between ligand and receptor.) Since Fodor, et al. teaches (col. 17, lines 4-7) that binding constants determined by their method assume that the tethering of the ligand does not affect the on-rate then the maximized affinities would result from a minimization of the off rate. The surface charge, Stokes radii, hydrophobicity and other properties of the dye-conjugated receptor are likely to be different than that of the naturally occurring receptor; hence the off rates will be different. Thus, one skilled in the art would appreciate that the optimal linker length discovered by the method of Fodor, et al. would be different than that for the naturally occurring receptor. The method disclosed by Fodor, et al, would allow one to investigate binding between ligands and labeled receptors, and the necessity for optimization of linker length and chemical composition between each ligand-labeled receptor pair. Alternatively, the present application teaches the tether length for a ligand directed toward a specific intracellular (and unlabeled) protein analyte, allowing for detection by intrinsic fluorescence.

Waskiewicz, et al. (EP 0 286 434) teaches the detection of viable ***microorganisms*** by (1) lysis of the microorganism using enzymes and/or detergents, and (2) detection of the dehydrogenase enzyme activity (abstract; pg. 1, lines 4-6, 35-38; pg. 3, lines 12-14).

(Dehydrogenase enzymes are ubiquitous to nearly every living microbial cell.) Trudil, et al. (US 6,395,504) teaches the detection of ***microorganisms*** by (1) lysis of the microorganism using the enzyme lysin (an enzymatic reagent derived from a bacteriophage infection of other bacteria), and (2) detection of the metabolite ATP released from the microbe via the luminescence generated from the luciferase reaction (col. 2, lines 62-65; col. 3, lines 1-4 & 15; col. 11, lines 40-47). (Trudil, et al. does not teach the use of bacteriophage infection to lyse microbial membranes; it teaches only the use of an enzyme from certain kinds of bacteriophage.) Both Waskiweicz, et al. and Trudil, et al. detect viable microbes (not any specific proteins) through materials that are ubiquitous to microorganisms (the enzyme dehydrogenase and the metabolite ATP, respectively). Neither method would be able to identify any specific protein inside a microbial analyte. (There are numerous dehydrogenase enzymes present in each bacterium or fungus. For illustration, Galperin et al. in "Analogous enzymes: Independent inventions in enzyme evolution" [Genome Research 8:779-790 (1998)] identifies 10 major classes of dehydrogenase enzymes, and 19 different specific dehydrogenase enzymes in E. coli.)

Responding to the double patenting rejections, Applicants respectfully point out: Claim 1 has been changed to describe a method that allows the identification of a protein that is contained inside a microbe (and thus not able to bind to tethered peptide ligands when the microbe is intact). This distinction is included in the preamble of claim 1 to distinguish it from claims 1, 9, 21, 23, and 30 of U.S. Patent 6 780,602; claims 21-23, and 26 of copending Application No. 10/706,547; and claims 38, 39, 41 and 47 of copending Application No. 10/706,542.

It is believed the claims are now in condition for allowance, which action is respectfully requested. Should the Examiner have any questions, he is requested to call Applicants' undersigned attorney collect at (801) 521-3200.

Respectfully submitted,

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CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that the attached Amendment is being facsimile-transmitted to Examiner Zachariah Lucas, Commissioner for Patents, Washington, D.C. fax (703) 872-9306 on the 12th day of April, 2005.

Roberta M. Kelly